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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,416	ANSARI, ASEEM Z.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 26 February 2007.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-38 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-38 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 16 January 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1, 12, 21, 30-36 and 38 have been amended in the response filed 2/26/2007. Claims 1-38 are under examination.

Claim Objections

Claims 25-26 and 37 are objected to because of the following informalities: there is a duplication of the word "step" in claims 25-26. Claim 37 recites "the method of claim 35" but claim 35 is drawn to a kit. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

It is noted that claims 1 and 22 have been amended to remove the limitation of "artificial" regulatory factors, therefore the rejection of claims 1-12 and 22-30 under 35 U.S.C. 112, second paragraph, as being indefinite for the limitation of "artificial" regulatory factors is withdrawn.

Claims 12, 21, 30, 34 and 38 are vague and indefinite because they recite the phrase "entropically destabilized" and the metes and bounds what constitutes an "entropically destabilized" linker are not clear. The metes and bounds of an entropically stable linker are not clear, so that the skilled artisan would know whether the linker is "entropically destabilized" in order to meet the limitation of the claims.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below.

Applicants submit that the phrase "entropically destabilized" is both explicitly defined in the specification and is readily understood by one of skill in the art. Entropy, of course, is a thermodynamic value. It is one of the factors that determine the free energy of a system. As used in the present claims, the phrase "entropically destabilized" is explicitly linked to a positively recited outcome, namely that the linker moiety confers conditional behavior upon the isolated nucleic acid target. The linker behaves in one fashion at a first temperature, and behaves in a second, distinct fashion at a second temperature different than the first. As a general proposition, "entropically destabilized," simply means that the linker is flexible. In particular, see the application as filed at page 25, lines 18-28. Applicant submits that the term "entropically destabilized" is sufficiently well described in the specification such that a person of ordinary skill in the art knows whether a linker meets the limitation of being "entropically destabilized." As noted in the above passage, to be considered "entropically destabilized," the linker must function as a "chemical switch."

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Although Applicants submit that an entropically destabilized linker behaves in one fashion at a first temperature, and behaves in a second, distinct fashion at a second temperature different than the first, the metes and bounds of how destabilized it must be to meet the limitation of entropically destabilized is not clear. For example, the skilled artisan would not know if a linker that is very slightly more flexible

at a temperature that higher by one degree would meet the limitation of an entropically destabilized linker that confers conditional behavior on the target. By some small degree, a change in flexibility induced by one degree of temperature change might confer conditional behavior. It is not clear if this is what Applicants intend as a limitation of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-10, 13-19 and 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Ansari et al (2001, Chem. Biol. Vol. 8, pages 583-592, online pub. 5/8/2001).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below.

In the submitted REMARKS, pages 12-16 (filed 2/26/2007), Applicants provide some background information, briefly explain Exhibits A-D and discuss transcription. Applicants submit that the Ansari et al paper describes an artificial transcription factor. See section 1.2 of the Ansari et al. paper, starting at page 584, right-hand column. Applicants submit that in the Ansari et al paper, the authors constructed an artificial transcription factor that consisted of a polyamide DNA-binding domain (designed to bind to the sequence 5'-TGTTAT-3'), a flexible tether, and one of three different activation domains based on VP16, a viral protein. A schematic diagram of this artificial transcription factor is shown in Fig. 1 of the Ansari et al. paper (at page 584) and in Exhibit B, attached hereto. Applicants submit that as shown in Exhibit B, Ansari et al's artificial transcription factor very closely mimics a real transcription factor. Applicants submit that there are three critical distinctions between the artificial transcription factor taught by Ansari et al, and the method and composition of matter recited in the present claims:

1) Applicants submit that the present claims do not recite an artificial transcription factor.

2) Applicants submit that the artificial transcription factor described in Ansari et al includes a polyamide DNA-binding domain that binds within the actual DNA recognition domain for the natural transcription factor (See section 2.5, at page 590 and section 4.3 at page 591) which describes the construction of the DNA target used for the *in vitro* transcription experiment described in Ansari et al. Applicants submit that the DNA target was fabricated with the appropriate palindromic recognition sequences for the

polyamide DNA-binding domains of Ansari's artificial transcription factor. Applicants submit that these palindromic recognition sequences were then purposefully placed in the proper orientation with respect to a downstream TATA box. Applicants submit that Ansari's *in vitro* transcription assay used a target DNA wherein the artificial transcription factor was explicitly designed to bind within an actual binding site (and thus to initiate transcription via an interaction with the transcription machinery itself).

3) Applicants submit that the artificial transcription factor of Ansari et al is explicitly designed to interact directly with "targets in the transcription machinery." See page 588, right-hand column, 1st paragraph. Applicants submit that to accomplish that goal, Ansari et al (see page 589) used a longer tether (or incorporated an internal pyrrole residue into an otherwise short tether) to project the activation domain away from the DNA (so that the activation domain can more easily interact with the transcriptional machinery). Applicants submit that the present invention does not recite an activation domain at all. In other words, Ansari et al. do not describe a construct that interacts with a gene-specific transcription factor or a regulatory factor. Ansari et al. describe an artificial transcription factor itself.

Applicants submit that the present claims positively require two elements that are not described in the Ansari et al paper. First, the nucleic acid target of the present invention has bound to it an anchor moiety. However, unlike the Ansari et al. paper, the anchor moiety in the present invention is bonded to the nucleic acid at a point "proximate to, but not within" the binding site for a regulatory factor. Applicants submit

that the artificial transcription factor of Ansari et al must bind within the corresponding binding site on the DNA target to be transcribed.

Second, Applicants submit that the present method uses a construct that interacts not with the transcription machinery (as in Ansari et al.), but with a regulatory factor (such as a transcription factor or other nucleic acid-binding molecules). See Exhibits C and D.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Responding to Applicants arguments as presented:

1. As written, the claims do not exclude an artificial transcription factor.

2. The claims have been examined using the broadest reasonable interpretation. For example, claim 1 step (a) recites:

"providing an isolated nucleic acid target that defines at least one known or putative binding site for a regulatory factor, the nucleic acid target having conjugated or covalently bonded thereto, at a point proximate to, but not within, the binding site".

The specific boundaries of the "known or putative binding site" are not specified and "a point proximate to" is not specifically defined. The recited regulatory factor is not specifically limited.

Ansari et al does teach an experiment in which 78bp templates were fabricated having several cognate binding sites 5'-TGTTAT-3' for the transcriptional activator (see Figure 7) in the context of a plasmid pAZA812 with an AdML TATA box 30 bp upstream of a 277 bp G-less cassette, for example. The assay comprises the addition of the activator compound and also yeast nuclear extract (see page 591, left column section

4.3). As mentioned above, limitation of "binding site", "proximate to" and "regulatory factor" can be interpreted broadly. Therefore the plasmid construct comprising the constructed cognate binding sites upstream from the TATA box would define at least one known or putative binding site for a regulatory factor such as a general transcription factor that would be found in the yeast nuclear extract added to the assay. Absent evidence to the contrary, some transcription factors would bind to the region outside of the constructed cognate binding sites, such as the segment next to the construct binding sites (i.e. the 40 bp section and the TATA box). Therefore, the constructed cognate binding sites for the artificial transcriptional activator would be proximate to but not within the binding site for a regulatory factor that binds on upstream of the TATA box. Therefore, the artificial activator bound to the constructed cognate binding sites upstream of a TATA box would meet the limitation of the compositions of claims 31-32.

3) Although Applicants submit that the instant invention does not recite an activation domain and Ansari do not describe a construct that interacts with a gene specific transcription factors or a regulatory factor, Ansari et al teach that transcriptional activators recruit transcriptional machinery to a proximal promoter to stimulate gene expression. Ansari et al also teach that activators "achieve specificity in targeting gene by a DNA recognition module which binds to cognate DNA sequences near a promoter". Ansari et al teach that the activating region binds several components of the transcriptional machinery, many components of which are large multi-subunit complexes associated with RNA Polymerase II (see page 583, for example). Using the broadest reasonable interpretation of the claims, the activation domain of the synthetic

activator reads on a test compound bonded to the linker moiety since it would contact large multi-subunit complexes associated with RNA Pol II (i.e. transcriptional machinery) and modulate the binding of these regulatory factors to nucleic acid binding sites. The artificial transcription activator taught by Ansari et al meets the limitation of an anchor moiety, a linker moiety and a test compound (e.g. an activation domain).

Applicants appear to be making the argument that "transcription machinery" as disclosed in Ansari et al is different from transcription factors, regulatory factors or other nucleic acid binding molecules. The skilled artisan would know that the multi-subunit complexes associated with RNA polymerase II comprise various transcription factors. Since the artificial transcription activators bind to and recruit transcriptional machinery, and the artificial transcription activators comprise a DNA binding region, a linker and a transcriptional activation domain (reads on a test compound), the teaching of Ansari et al does meet the claimed limitations in the broadest reasonable interpretation.

Claims 22-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Ansari et al (2001, Chem. Biol. Vol. 8, pages 583-592, online pub. 5/8/2001) as evidenced by Sadowski et al (Nature, 1998, Vol. 335, pages 563-564).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below.

Applicants full arguments regarding this rejection in particular appear in REMARKS filed 2/26/2007, pages 16-18. Applicants submit that the arguments with respect to Ansari et al are discussed in detail above. Applicants submit that it is

especially critical to note that Sadowski et al do not teach or suggest that the GAL4-VP16 is a transcription activator that can modulate binding of natural, gene-specific transcription factors (not general transcription factors), as alleged at the bottom of page 7 of the Office Action. (Applicants submit that the Office provides no pin-point citation for this conclusion). Applicant notes that the binding sites for the GAL4 portion of Sadowski's construct were purposefully engineered into the CHO cells. Those binding sites are not present in the native CHO cells. See page 563, right hand column, first full paragraph of Sadowski et al: "Reporter plasmids are distinguished by the presence (or absence) of insertions in the yeast sequence UAS_0 that contains four GAL4 binding sites." Thus, Applicants submit Sadowski engineered the binding sites on the DNA target into their construct, and then positioned the binding sites at various locations relative to the gene to be transcribed. Applicants submit that Sadowski do not teach or suggest that their GAL4-VP16 modulates the binding of natural gene specific transcription factors to their corresponding natural binding sites.

Applicants submit that Sadowski et al do not describe any type of linker between the GAL4 and the VP16 portion of their construct. Applicants submit that Sadowski et al explicitly state that the activation activity of GAL4-VP16 is unlikely to be increased binding and cite Page 564 left column, 2nd paragraph. Applicants also submit that in both Ansari et al and Sadowski et al, the construct interacts with the transcription machinery itself, rather than with a gene-specific regulatory factor, such as a transcription factor. The distinction is illustrated in Exhibit B, which shows schematically

the Ansari et al-Sadowski et al. combination, as compared to Exhibits C and D, which schematically illustrate the present invention.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. The arguments regarding binding of an anchor outside the binding site for a transcription factor or a regulatory factor has been discussed above.

It appears that some of Applicant's arguments are based on modulation of binding of gene-specific transcription factors and not general transcription factors. It should be noted that the claims do not recite the limitation of modulating binding of **gene specific** transcription factors. There is no limitation recited in the claims to exclude general transcription factors from the claimed inventions. The Examiner did not allege gene-specific transcription factors at the bottom of page 7 of the Office Action.

It is important to note in the discussion of this rejection that Sadowski et al was used as a supporting reference to provide evidence that the VP16 portion of the transcriptional activator is a strong transcriptional activator in CHO cells and can modulate binding of natural transcription factors such as those found in culture CHO cells. Sadowski et al teach that VP16 attaches to one or more host encoded proteins that recognize DNA sequences in their promoters (see page 563, right column, 1st paragraph, in particular). Absent evidence to the contrary, host encoded proteins that recognize DNA sequences are "natural transcription factors". In Sadowski et al, it appears that the host encoded proteins come from the CHO cells. Ansari et al use yeast nuclear extracts in their *in vitro* transcription assays. Again, absent evidence to the contrary, transcription factors in yeast nuclear extracts would be "natural transcription

factors". Therefore, Sadowski et al provides evidence that the VP16 portion of the transcriptional activator taught in Ansari et al would modulate binding of natural transcription factors found in the *in vitro* assay.

Although Applicants argue that the binding sites for the GAL4 portion of Sadowski's construct were purposefully engineered into the CHO cells and are not present in the native CHO cells and Sadowski do not teach or suggest that their GAL4-VP16 modulates the binding of natural gene specific transcription factors to their corresponding natural binding sites, it is important to note that as the claims are written, the limitation is that the transcription factors are natural. The claims do not limit the transcription factor binding site to be natural. For example claim 22 step (a) (iii) recites "wherein the test compound is known to modulate binding of natural transcription factors to the transcription factor binding site defined in the nucleic acid target". The instant specification does not provide a limiting definition of "natural" transcription factors. The claim limitation can be interpreted broadly so that "natural" transcription factors would be those found in nature.

Although Applicants submit that Sadowski et al do not describe any type of linker between the GAL4 and the VP16 portion of their construct, the purpose of the Sadowski et al reference in this rejection is to provide evidence regarding an inherent characteristic of the VP16 element and not as a reference in a 35 USC 103 rejection. Therefore Sadowski et al do not need to describe any type of linker between the GAL4-VP16 construct. The construct comprised of an anchor moiety, linker moiety and a test

compound as an artificial transcription activator and is supplied by Ansari et al and has been previously discussed.

Although Applicants submit that Sadowski et al explicitly state that the activation activity of GAL4-VP15 is unlikely to be increased binding,, it appears that the binding being referenced in the cited passage is the binding of the GAL4 to the DNA. In the same paragraph Sadowski et al also teach that,

> "we imagine that the acidic region of VP16 interacts with unusual avidity with some component of the transcriptional apparatus, perhaps the TATA binding factor TFIID".

Although Applicants again submit that in both Ansari et al and Sadowski et al, the construct interacts with the transcription machinery itself, rather than with a gene-specific regulatory factor, such as a transcription factor, it should be noted that "gene-specific" regulatory factor and not a general transcription factor is not a limitation recited in the claims.

Claims 1-4, 8-9, 11, 13, 17-18, 20, 31, 33, 35 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanojevic (U.S. Patent Application Pub. No. 2003/105045, filed 3/14/2002).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below.

Applicants' full arguments regarding this rejection in particular appear in REMARKS filed 2/26/2007, pages 18-21. Applicants traverse because the Stanojevic publication, like the Ansari et al. paper, is limited entirely to a description of artificial

transcription factors. Applicants submit that the DNA-binding domain as described in Stanojevic is purposefully designed to bind within the binding site for a transcription factor. Applicants submit that all of the present claims require that the recited construct include an anchor moiety that binds at a point proximate to, but not within, the regulatory factor binding site. Applicants submit that more specifically, the Stanojevic publication is clearly directed to artificial transcription factors (ATFs). Applicants cite paragraph 10 of Stanojevic, where Stanojevic notes that his ATFs are modular, and include a DNA-binding domain and an effector domain. Applicants submit that Stanojevic's main goal, as articulated in paragraph 10, is to introduce new, drug-like properties into the ATF's, while still maintaining their ability to regulate RNA transcription of specific genes. Applicants submit that of particular note is that, like the Ansari et al paper discussed above, the ATF described by Stanojevic must bind within a promoter binding site in order to function as a transcription factor. Applicants quote paragraph 41 of the Stanojevic publication. (See page 19 of REMARKS).

Applicants submit that Stanojevic's construction is an artificial transcription factor and that the present claims are not directed to an artificial transcription factor. Applicants quote paragraph 55 of the Stanojevic publication (See page 19 of REMARKS) and submit that it discusses his artificial transcription factors in the context of ATFs that suppress transcription, rather than activate it.

Applicants submit that Stanojevic's ATF thus clearly functions in the same fashion as a natural transcription factor: they bind within the promoter recognition site, where they then interact with the transcriptional machinery itself. Applicants submit that

this is totally different from the present claims, which positively require that the anchor bind at a point outside the binding site for the regulatory factor.

Applicants note that Stanojevic, like Sadowski, uses a test system that simply incorporates suitable binding sites at appropriate locations relative to the gene to be transcribed. Applicants cite Figs. 3A and 3B of Stanojevic and quote paragraph 57 of the Stanojevic publication (See page 20 of REMARKS). Applicants submit that as is made clear from this passage, Stanojevic's ATF is purposefully designed to bind within the promoter region itself- that is, within binding site for a regulatory factor. Applicants submit that in contrast, Claim 1, for example, explicitly requires that the nucleic acid target include an anchor moiety that is bonded at a point proximate to the regulatory factor binding site, but not within the binding site. Applicants submit that because Stanojevic's approach is to make an entire ATF (as illustrated in Exhibit B), Stanojevic's ATF is purposefully designed to bind within the binding sites utilized by natural transcription factors.

Applicants quote paragraph 96 of the Stanojevic publication (See pages 20-21 of REMARKS), which addresses Stanojevic's view about why his ATFs could be more potent than the GAL4-VP16 construct. Applicants submit that as noted in this passage, Stanojevic's ATF is designed to bind within the promoter region itself, so that the effector portion of the construct can interact directly with the transcription machinery (i.e., the RNA Pol II enzyme complex). Applicants submit that in contrast, the present claims use a construct purposefully designed to bind outside of the regulatory factor-binding site. Applicants submit that the last step of Claim 1 positively requires a

determination of whether the binding of the regulatory factor to its binding site defined in the nucleic acid target is modulated by presence of the test compound. Applicants submit that Stanojevic's approach does not include any such step because Stanojevic is not looking at modulating the binding of a regulatory factor (such as a **gene-specific** transcription factor) to its binding site on the DNA target. Applicants submit that Stanojevic describes an entire artificial transcription factor *per se*. Applicants submit that Stanojevic's ATF binds within the promoter region and either up-regulates or down-regulates transcription based on the nature of the effector domain included in the ATF. Applicants submit that the present claims, however, are not directed to ATFs, but rather to constructs that modulate the binding of regulatory factors (such as gene-specific transcription factors) to their cognate binding sites on a DNA target.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. The argument based on the submission that Stanojevic teach artificial transcription factors and therefore do not meet the claim limitation is not persuasive because artificial transcription factors are not excluded from the claimed inventions. The ATFs described by Stanojevic meet the limitations of a construct with an anchor moiety, a covalently bonded linker moiety and a test compound. Although in some embodiments the DNA-binding domain may be designed to bind within the binding site for a transcription factor, there are other contemplated embodiments that do not require binding at the binding site for a transcription factor. For example, Stanojevic teach an embodiment in which the binding site for the test composition is located within 100 base pairs of the site for initiation of transcription (see paragraph 0021). Stanojevic

disclose that a transcription effecter is a composition which causes an increase in RNA synthesis when present “in the vicinity” of a promoter and can act “ near” or at the site of transcription initiation (see paragraphs 0034-0034). As taught by Stanojevic and quoted by Applicants, paragraph 41 discloses that the DNA binding domain recognizes a site that is typically positioned relatively near to the transcriptional start site of the gene for which the activator can affect transcription, although some activators may be able to act over long distances. Many activators or repressors are able to act over long distances and use of these effectors is contemplated in the invention.

Using the broadest reasonable interpretation of the claim limitations, the embodiments in which the ATF binds at a site “located within 100 base pairs of the site for initiation of transcription” or is “in the vicinity” of a promoter and can act “ near” or at the site of transcription initiation or is “positioned relatively near to the transcriptional start site” or “are able to act over long distances”, meets the limitation of a point proximate to but not within the transcription factor binding site. Artificial transcription factors are not excluded from the claimed inventions, and the constructs taught by Stanojevic meet the claim limitations as detailed in the previous Office action.

Applicants submit that paragraph 55 of the Stanojevic publication discusses artificial transcription factors in the context of ATFs that suppress transcription, rather than activate it. However, the claimed method is drawn to modulation of regulatory factor binding, which includes activation as well as repression. Furthermore, repression is only one embodiment in the Stanojevic publication.

Although Applicants submit that in paragraph 96 of the Stanojevic publication passage, Stanojevic's ATF is designed to bind within the promoter region itself, so that the effector portion of the construct can interact directly with the transcription machinery, this is only one embodiment in the Stanojevic publication. The other contemplated embodiments in which the binding site is proximate to a binding site for a regulatory factor have been discussed herein above.

Regarding Stanojevic paragraph 0096, Applicants submit that Stanojevic's approach does not include a step for determination of whether the binding of the regulatory factor to its binding site defined in the nucleic acid target is modulated by presence of the test compound as in instant claim 1 because Stanojevic is not looking at modulating the binding of a regulatory factor (such as a gene-specific transcription factor) to its binding site on the DNA target. However, as mentioned previously, the claims do not include the limitation that the regulatory factor must be a gene-specific transcription factor and does not exclude general regulatory factors.

In addition, a step for determination of whether the binding of the regulatory factor to its binding site defined in the nucleic acid target is modulated by presence of the test compound is contemplated in paragraph 0096 in which one embodiment of the ATF molecule is determined to facilitate the recruitment of a holoenzyme to the promoter and the initiation of RNA transcription. Determination of the amount of transcription facilitated by the test ATF compared to a control would constitute determination of whether the binding of the regulatory factor to its binding site defined in the nucleic acid target is modulated by presence of the test compound, since the one of

the actions of the ATF is to interact with the proteins involved in RNA transcription such as the TATA box binding proteins, RNA polymerase II holoenzyme. Stanojevic disclose that the interactions facilitate or inhibit the assembly of the transcriptional apparatus at the promoter and therefore activate or repress RNA synthesis encoding by the regulated gene (see paragraph 0005, in particular). Therefore the teachings of Stanojevic anticipate the claimed inventions.

Claims 1, 3-4, 8-10, 13, 15, 17-19, 22, 26-28 and 31-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Stanojevic and Young (Biochem 2002, Vol. 41 pages 7209-7216).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below.

Applicants' full arguments regarding this rejection in particular appear in REMARKS filed 2/26/2007, pages 21-23. Applicants traverse on essentially the same grounds articulated in the prior section of this response. Applicants submit that the Stanojevic & Young paper is limited to a description of artificial transcription factors (ATFs) and the present claims are not directed to ATFs, but to constructs that modulate the binding of a regulatory factor (such as a transcription factor) to its corresponding binding site on a DNA target. Applicants submit that the present claims positively require that the anchor moiety bind at a point proximate to a regulatory factor binding site, but not within that binding site.

Applicants submit that the Stanojevic & Young paper describes an ATF that binds within a corresponding promoter region (i.e., within a corresponding regulatory factor binding region) in the target DNA. Applicants cite Stanojevic & Young at page 7210, right column, last paragraph and Figs. 3A and 3B. The passage at page 7210 explicitly states:

"As a DNA-binding domain, we utilized the 22-mer triplex-helix-forming oligonucleotide (TFO). The TFO's have been used to target specific DNA sequence and <u>sites in gene promoters</u> for over a decade [citations omitted]. "

Applicants submit that Figs. 3A and 3B are schematic diagrams of the control transcription template and the ATF transcription template, respectively. Applicants submit that the control template contains five GAL4 binding sites <u>incorporated into the promoter region</u>. Applicants submit that the ATF transcription template contains five ATF binding sites instead of the GAL4 binding sites. Applicants summarize that Stanojevic & Young created a transcription model that included a binding site for the ATF engineered directly into the target DNA at an appropriate position relative to the TATA box shown in the figures. Applicants submit that Stanojevic & Young's ATF bound within that regulatory factor binding site.

Applicants submit that the sites were purposefully created by Stanojevic & Young so that their ATF would have a place to bind. In short, Stanojevic & Young created both an ATF, and a corresponding binding site for the ATF. If the corresponding binding site for Stanojevic & Young's ATF is omitted, the construct fails to function. Applicants cite Stanojevic & Young at page 7212, right-hand column.

Applicants submit that in contrast the present claims positively require that the construct bind proximate to, but not within, the regulatory factor binding site. Applicants submit that this positive limitation of the claims is neither described, nor suggested by the Stanojevic & Young paper, and Stanojevic & Young explicitly teach providing the regulatory factor binding site itself, as well as an ATF that binds in a sequence-specific fashion to the regulatory factor binding site.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. The point regarding the present claims not being directed to artificial transcription factors is detailed in the above discussion. Artificial transcription factors are not excluded in the claims as written.

Regarding the cited passage at page 7210, right column, it appears that Stanojevic & Young are describing TFO in general as having been used to target specific DNA sequences and sites in gene promoters.

Stanojevic & Young do appear to have engineered template constructs as shown in Figure 3. However Stanojevic & Young also teach that the construct comprises the minimal HSV-tk promoter driving the expression of a CAT reporter gene. The five direct repeats of ATF-binding sequence were inserted into the polylinker lying immediately upstream of the promoter to yield the template (see page 7212, right column, and page 7210, right column 3rd paragraph, for example). Stanojevic & Young teach that transcription initiated from the same +1 site in the promoter adjacent to the TATA box (see page 7212, right column). Stanojevic & Young also teach that the potency of the ATF molecules may be due to the extended chemical structure that leaves the

activation domains much more exposed to interaction with the RNA polymerase holoenzyme and other proteins. The exposed activation domain would in effect facilitate the recruitment of the holoenzyme to the promoter and the initiation of the RNA transcription.

Contrary to Applicants submission, the ATFs taught by Stanojevic & Young meet the structural limitations of a construct having an anchor moiety, a linker moiety and a bonded compound (activation or effectors domain). There is no limitation in the claims limiting the regulatory or transcription factor to gene specific factors, and no limitation in the claims excluding general transcription factor binding as being modulated.

As discussed above, the claimed limitation of "providing an isolated nucleic acid target that defines at least one known or putative binding site for a regulatory factor, the nucleic acid target having conjugated or covalently bonded thereto, at a point proximate to, but not within, the binding site" is being given the broadest reasonable interpretation because the phrase "binding site for a regulatory factor" is not given a limiting definition. One of ordinary skill in the art would recognize that transcription could be modulated from multiple sites along the nucleotide sequence. The term "promoter" as used in the art can often include multiple elements and may include a binding site for more than one regulatory factor. RNA polymerase holoenzyme and other proteins are critical parts of the transcription process. The structures taught by Stanojevic & Young are disclosed to interact with the RNA polymerase holoenzyme complex. Absent evidence to the contrary, the RNA polymerase holoenzyme complex would bind close to or on the TATA box. If the ATF as taught by Stanojevic & Young are in the promoter adjacent to the

TATA box (i.e. proximate to), and are interacting and modulating the RNA polymerase holoenzyme complex, then the teaching of Stanojevic & Young meets the limitation of at least one known or putative binding site for a regulatory factor, the nucleic acid target having conjugated or covalently bonded thereto, at a point proximate to, but not within, the binding site"

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 11, 13, 20, 31 and 33 are rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001, Chem. Biol. Vol.8, pages 583-592, online pub. 5/8/2001) in view of Arora et al (J. Am. Chem. Soc. 2002, Vol 124, pages 13067-13071).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below.

Applicants' full arguments regarding this rejection in particular appear in REMARKS filed 2/26/2007, pages 23-25.

Applicants traverse because the combination of Ansari et al and Arora et al. results in an ATF of the type described by Ansari et al, using the poly-L-proline linker

described in Arora et al. Applicants submit that the outcome is simply another type of ATF that is specifically designed to bind within the regulatory factor binding site in the target DNA and then to interact, via an activation domain, with the transcription machinery itself. Applicants cite Figure 1 of the Arora et al, which is a schematic diagram of Arora's ATF. Note that Fig. 1 of Arora et al is substantially identical to Exhibit B submitted herewith and discussed earlier. Applicants submit that the combination of Ansari et al with Arora et al thus yields an ATF having the DNA-binding domain and effector domains as described in Ansari et al, coupled with the poly-L-proline linker described in Arora et al.

Applicants submit that in both Ansari et al and Arora et al, the DNA-binding domain of the ATF is purposefully designed to bind within the corresponding regulatory factor binding site present on the DNA target. This is best shown in Fig. 1 of Arora et al. Applicants submit that the ATF described by the combination of Ansari et al. with Arora et al does not interact with other transcription factors, but initiates transcription by a direct interaction of the activation domain of the ATF with the transcription machinery. Applicants submit that as noted above with respect to Ansari et al taken alone, there are two critical distinctions between the ATF taught by the combination of Ansari et al. and Arora et al., and the method and composition of matter recited in the present claims. The combination of these two references yields an ATF essentially identical to Ansari's ATF, but with Arora's poly-L-proline linker. Applicants submit that Arora et al. is largely cumulative to the teaching of Ansari et al. Applicants cite Ansari et al (page 590 section

2.5 and page 591 section 4.3), which describes the construction of the DNA target used for the *in vitro* transcription experiment described in Ansari et al.

Applicants submit that the DNA target in both Ansari et al and Arora et al was fabricated with the appropriate palindromic recognition sequences for the polyamide DNA-binding domains. Applicants submit that these palindromic recognition sequences were then purposefully placed in the proper orientation with respect to a downstream TATA box. Applicants submit that in both Ansari et al. and Arora et al, an in vitro transcription assay was used wherein the ATF was explicitly designed to bind within an actual binding site (and thus to initiate transcription via an interaction with the transcription machinery itself). Applicants cite page 13068, right-hand column of Arora et al. Applicants submit that the ATFs of Ansari et al combined with Arora et al are explicitly designed to interact directly with "targets in the transcription machinery" and that both used a specific type of tether to project the activation domain away from the DNA (so that it can more easily interact with the transcriptional machinery).

Applicants reiterate the previous submissions that the present method does not use an artificial transcription factor, but employs a construct that interacts with a gene-specific transcription factor (or other regulatory factor). Applicants reiterate the previous submissions that the present claims positively require the anchor moiety in the present invention to be bonded to the nucleic acid at a point "proximate to, but not within" the binding site for a regulatory factor. Applicants reiterate the previous submissions that the present method uses a construct that interacts not with the transcription machinery (as in Ansari et al. and Arora et al.), but with a regulatory factor (such as a gene-

specific transcription factor). Applicants refer to Exhibits C and D, which illustrate schematically the method of Claim 1.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Applicants' arguments regarding Ansari et al have been extensively discussed above (pages 4-9 of this document). As mentioned previously, the claim limitations do not exclude artificial transcription factors as the claimed construct comprising an anchor, linker moiety and test compound, wherein the test compound is the activation domain.

The Arora et al reference combined with Ansari et al renders obvious the claimed methods and composition wherein the linker moiety is at least 30 Å long because a linker region of 36-45 Å optimizes transcriptional activation. In Figure 1 of Arora et al, the activation domain is pictured contacting the RNA pol II holoenzyme complex, presumably in order to recruit the transcriptional machinery to the nearby promoter (see 1st paragraph, page 13067). As discussed above, as written the claims do not recite the limitation of interaction with a gene specific transcription factors and therefore using the broadest reasonable interpretation, elements of the general transcription machinery (RNA pol II holoenzyme complex) would meet the limitation of a regulatory or transcription factors to be modulated by a test compound. Therefore Ansari et al (2001) in view of Arora et al render obvious the claimed methods and compositions.

Claims 1, 3, 6-9, 13 and 15-18 are rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001, Chem. Biol. Vol.8, pages 583-592, online pub.

5/8/2001) in view of Ansari et al (2002, Curr. Opin. Chem. Biol. Vol. 6, pages 765-772).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below. Applicants' full arguments regarding this rejection in particular appear in REMARKS filed 2/26/2007, pages 25-28. Ansari et al. (2001) has been addressed in several prior sections of this response. Applicants incorporate those prior remarks herein by reference. Applicants also briefly recap the Ansari et al. (2001) paper.

Applicants submit that there are three critical distinctions between the artificial transcription factor taught by Ansari et al. (2001), and the method and composition of matter recited in the present claims. First, as noted earlier, the present claims are not directed to ATFs. Second, the ATF described in Ansari et al. (2001) includes a polyamide DNA-binding domain that binds within the actual DNA recognition domain for the natural transcription factor. See Ansari et al., section 2.5, at page 590. See also section 4.3 of the Ansari et al. (2001) paper (at page 591). Thus, Ansari's in vitro transcription assay used a target DNA wherein the ATF was explicitly designed <u>to bind within an actual binding site</u> (and thus to initiate transcription via an interaction with the transcription machinery itself). Third, the ATF of Ansari et al (2001) is explicitly designed to interact directly with "targets in the transcription machinery." See Ansari et al (2001) at page 588, right-hand column, first full paragraph. Applicants submit that in other words, Ansari et al (2001) do not describe a construct that interacts with a gene-specific

transcription factor or a regulatory factor, but describe an artificial transcription factor itself.

Applicants submit that combining Ansari et al (2001) with Ansari et al (2002) does not add any further teaching to the 2001 paper because the two papers are largely cumulative. Most notably, however, see the section in Ansari et al. (2002) titled "DNA-binding domain," starting at page 766, right-hand column. Applicants submit that the entire discussion in this section of the Ansari et al. (2002) paper is directed to DNA-binding domains "that target unique promoter sequences." Applicants submit that combining the two Ansari et al. papers yields an ATF that includes a DNA-binding domain that targets a unique promoter sequence (i.e., a transcription factor binding site).

Applicants reiterate the previous submissions that the present method does not use an artificial transcription factor, but employs a construct that interacts with a gene-specific transcription factor (or other regulatory factor). Applicants reiterate the previous submissions that the present claims positively require the anchor moiety in the present invention to be bonded to the nucleic acid at a point "proximate to, but not within" the binding site for a regulatory factor. Applicants reiterate the previous submissions that the present method uses a construct that interacts not with the transcription machinery (as in Ansari et al. and Arora et al.), but with a regulatory factor (such as a gene-specific transcription factor). Applicants refer to Exhibits C and D, which illustrate schematically the method of Claim 1.

Applicants submit that this arrangement of elements is patentably distinct from the ATFs described in combination of the two Ansari et al. papers. Applicants submit that the present claims thus require that a construct be bound to the target DNA at a point proximate to the binding site, but not within it.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Applicants' arguments regarding Ansari et al have been extensively discussed above (pages 4-9 of this document). As mentioned previously, the claim limitations do not exclude artificial transcription factors as the claimed construct comprising an anchor, linker moiety and test compound, wherein the test compound is the activation domain. Figure 1 in Ansari et al (2002) illustrates binding of an activator or repressor element upstream from where the RNA polymerase II complex would bind to the genomic DNA. Using the broadest reasonable interpretation of the claims, this would meet the limitation of "at least one known or putative binding site for a regulatory factor, the nucleic acid target having conjugated or covalently bonded thereto, at a point proximate to, but not within, the binding site"

As discussed above, as written, the claims do not recite the limitation of interaction with a gene specific transcription factors and therefore using the broadest reasonable interpretation, elements of the general transcription machinery (RNA pol II holoenzyme complex) would meet the limitation of a regulatory or transcription factors to be modulated by a test compound. Therefore Ansari et al (2001) in view of Ansari et al (2002) render obvious the claimed methods.

Claims 22 and 29 are rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001, Chem. Biol. Vol.8, pages 583-592, online pub. 5/8/2001) as evidenced by Sadowski et al, in view of Arora et al (J. Am. Chem. Soc. 2002, Vol. 124, pages 13067-13071).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below. Applicants' full arguments regarding this rejection in particular appear in REMARKS filed 2/26/2007, pages 28-30. Applicants submit that all of the Ansari et al (2001), Sadowski et al., and Arora et al. papers have been discussed in previous sections of this response and incorporate those comments are herein by reference. Applicants briefly recap the Ansari et al (2001) paper describes an artificial transcription factor. Applicants refer to attached Exhibit B.

Applicants submit that Sadowski et al do not teach or suggest that the GAL4-VP16 is a transcription activator that can modulate binding of natural transcription factor, as alleged at the bottom of page 7 of the Office Action. Applicants submit that the binding sites for the GAL4 portion of Sadowski's construct were purposefully engineered into the CHO cells. Applicants submit that those binding sites are not present in the native CHO cells and refer to page 563, right hand column, first full paragraph of Sadowski et al

Applicants submit that Sadowski engineered into their construct the binding sites on the DNA target, and then positioned the binding sites at various locations relative to the gene to be transcribed to engineer a suitable binding site for their ATF. But in every

instance, the GAL4 portion of the GAL4-VP16 construct binds to that specific binding site (which was inserted solely so that the GAL4-VP 16 fusion protein would have place to bind). Applicants submit that contrary to the assertion made by the Office, Sadowski et al. do not teach or suggest that their GAL4-VP 16 "modulates" the binding of natural transcription factors to their corresponding natural binding sites. See Sadowski et al. at page 566, left-hand column, first paragraph: "Activity was not detected in either cell line.., when the UAS_0 was positioned at -1180 or +1850, and in no case did GAL4 activate."

Applicants again submit that Sadowski et al. also do not describe any type of linker between the GAL4 and the VP16 portions of their construct. Applicants submit that the present claims are not directed to an artificial transcription factor. Applicants submit that the full, three-way combination of Ansari et al., Sadowski et al., and Arora et al. teaches a modular, three-part ATF that is purposefully designed to bind within a transcription factor binding site.

Applicants reiterate the previous submissions that the present claims positively require the anchor moiety in the present invention to be bonded to the nucleic acid at a point "proximate to, but not within" the binding site for a regulatory factor. Applicants reiterate the previous submissions that the present method uses a construct that interacts not with the transcription machinery (as in Ansari et al. and Arora et al.), but with a regulatory factor (such as a gene- specific transcription factor).

Applicants submit that the present claims thus require that a construct be bound to the target DNA at a point proximate to the binding site, but not within it.

Applicants submit that the artificial transcription factor of Ansari et al even when modified to include the GAL4 or the VP16 portions of Sadowski's construct, and the poly-L-proline tether of Arora et al. must bind within the binding site for the corresponding natural transcription factor-binding site. Applicants submit that Sadowski explicitly states that GAL4 binds within its corresponding regulatory binding site *in vivo*.

Applicants reiterate the previous submissions that the present method does not use an artificial transcription factor, but employs a construct that interacts with a gene-specific transcription factor (or other regulatory factor). Applicants submit that none of Ansari et al (2001), Sadowski et al., and Arora et al., taken alone or in any combination, disclose or suggest that the construct used in the method binds at a point proximate to, <u>but not within,</u> the transcription factor binding site (claims 22 and 29).

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Applicants' arguments regarding Ansari et al, Sadowski et al., and Arora et al have been extensively discussed above. The arguments regarding binding of an anchor outside the binding site for a transcription factor or a regulatory factor has been discussed above extensively. As mentioned previously, the claim limitations do not exclude artificial transcription factors as the claimed construct comprising an anchor, linker moiety and test compound, wherein the test compound is the activation domain.

As previously discussed the claims do not recite the limitation of modulating binding of gene specific transcription factors. There is no limitation recited in the claims to exclude general transcription factors from the claimed inventions.

In regards to Applicants argument concerning Sadowski et al, it should be noted that Sadowski et al was used as a supporting reference to provide evidence that the VP16 portion of the transcriptional activator is a strong transcriptional activator in CHO cells and can modulate binding of natural transcription factors such as those found in cultured CHO cells. Therefore Sadowski et al do not need to describe any type of linker between the GAL4- VP16 construct.

Sadowski et al teach that VP16 attaches to one or more host encoded proteins that recognize DNA sequences in their promoters (see page 563, right column, 1st paragraph, in particular). Absent evidence to the contrary, host encoded proteins that recognize DNA sequences are "natural transcription factors". In Sadowski et al, it appears that the host encoded proteins come from the CHO cells. While Ansari et al does not use host encoded proteins from CHO cells, Ansari et al use yeast nuclear extracts. Absent evidence to the contrary, transcription factors in yeast nuclear extracts would be "natural transcription factors". Therefore, Sadowski et al provides evidence that the VP16 portion of the transcriptional activator taught in Ansari et al would modulate binding of natural transcription factors found in the *in vitro* assay.

Although Applicants argue that the binding sites for the GAL4 portion of Sadowski's construct were purposefully engineered into the CHO cells and are not present in the native CHO cells and therefore Sadowski do not teach or suggest that their GAL4-VP16 modulates the binding of natural gene specific transcription factors to their corresponding natural binding sites, it is important to note that as the claims are written, the limitation is that the transcription factors are natural. The claims do not limit

the transcription factor binding site to be natural. The instant specification does not provide a limiting definition of “natural” transcription factors. The claim limitation can be interpreted broadly so that “natural” transcription factors would be those found in nature. Therefore, Ansari et al (2001) as evidenced by Sadowski et al, in view of Arora et al render obvious the inventions of claims 22 and 29.

Claims 22 and 24-27 are rejected under 35 U.S.C. 103(a) as being obvious over Ansari et al (2001) as evidenced by Sadowski et al (Nature, 1998, Vol. 335, pages 563-564) and in view of Ansari et al (2002).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below. Applicants' full arguments regarding this rejection in particular appear in REMARKS filed 2/26/2007, pages 30-33.

Applicants submit that all of the Ansari et al (2001), Sadowski et al., and Ansari et al (2002) papers have been discussed in previous sections of this response. Those comments are incorporated herein by reference. Applicants recap Ansari et al (2001) Applicants present the same argument as above regarding Sadowski et al. Applicants submit that the Ansari et al. (2002) paper does not add any further teaching to the Ansari et al (2001) and Sadowski et al papers because Ansari et al. (2002) is cumulative to Ansari et al. (2001). See, however, the section in Ansari et al. (2002) titled "DNA-binding domain," starting at page 766, right-hand column. The entire discussion in this section of the Ansari et al. (2002) paper is directed to DNA-binding domains "that

target unique promoter sequences." Applicants submit that combining the two Ansari et al. papers with Sadowski et al. yields an ATF that includes a DNA-binding domain that targets a unique promoter sequence (i. e., a transcription factor binding site).

Applicants submit that the present invention is not directed to an ATF. The construct required by the present claims includes an anchor that binds outside of the binding site for a transcription factor (or other regulatory factor). The combination of Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002), in contrast, describes an artificial transcription factor that binds within the binding site for a natural transcription factor.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive. Applicants' arguments regarding Ansari et al (2001), Sadowski et al., and Ansari et al (2002) have been extensively discussed above.

Applicant's arguments that the anchor moiety in the present invention is bonded to the nucleic acid at a point "proximate to, but not within" the binding site for a regulatory factor in regard to in the combination of Ansari et al. (2001), Sadowski et al., and Ansari et al. (2002) have been addressed in the above discussions of these references. Therefore, Ansari et al (2001) as evidenced by Sadowski et al, in view of Ansari et al. (2002) render obvious the inventions of claims 22 and 24-27.

Claims 1, 3, 8-9, 11, 13, 17-18, 20, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (U.S. Patent No. 6,165,720) in view of Arora et al (J. Am. Chem. Soc. 2002, Vol. 124, pages 13067-13071).

This rejection is being maintained for reasons of record in the previous Office Action, mailed 9/20/2006 and for reasons outlined below. Applicants full arguments regarding this rejection in particular appear in REMARKS filed 2/26/2007, pages 33-34.

Applicants submit that the Felgner et al patent describes an approach that is distinctly different from both the presently claimed invention, as well as the artificial transcription factors described in Arora et al. As noted at column 3, lines 24-45 of the Felgner et al patent, Felgner et al use a PNA-DNA hybrid vector, such as a plasmid. Applicants submit that the PNA portion of the plasmid can be bound to a peptide or protein moiety, such as the activator domain of transcription factor. Applicants note that Felgner et al do not describe including a moiety that interacts with transcription factors in the construct. Applicants submit that the activator domain of a transcription factor (natural or artificial) interacts directly with the transcription machinery (the RNA Pol II complex), not endogenous transcription factors themselves. This is explicitly taught in the Arora et al. reference. See Fig. 1 of Arora et al. and the accompanying description.

Applicant traverses this rejection because the combination of Felgner et al with Arora et al yields a PNA-DNA plasmid having attached thereto a linker as taught by Arora et al, at the end of which is attached a transcription activator domain. Applicants submit that the construct lacks the required relationship between the location of the anchor moiety, and the location of the regulatory factor binding site. In short, Applicants submit that Felgner et al's approach can only evaluate compounds for their ability to act as an <u>activator domain</u> that interacts directly with the transcription machinery, and not

with gene-specific transcription factors themselves. Applicants submit that the present claims positively require "**determining whether binding of the regulatory factor to the binding site defined in the nucleic acid target is modulated by the presence of the test compound.**" Applicants submit that the Feigner's construct lacks both a regulatory factor binding site defined in the PNA-DNA construct, as well as any ability to modulate binding of a regulatory factor to the non-existent target site.

Applicants submit that in Felgner et al 's approach, a test compound that is a putative transcription activation domain is linked to the PNA portion of the plasmid (via Arora et al.'s linker). Applicants submit that if the test compound functions as a transcription activator domain, it will interact directly with the RNA Pol II complex (as explicitly shown in Fig. 1 of Arora et al.). Applicants submit that Feigner's test compound will not modulate binding of a regulatory factor to the binding site defined in the PNA-DNA vector because: (1) Feigner et al. do not define such a binding site in their plasmid, and (2) Feigner et al only mention activation domains - compounds that react with the transcription machinery itself, not gene-specific regulatory factors, such as transcription factors.

Applicant's arguments filed 2/26/2007 have been fully considered but they are not persuasive.

Although Applicants submit that Felgner et al use a PNA-DNA hybrid vector, such as a plasmid, this is only one embodiment of the invention, in other embodiments the nucleic acid molecule is linear single or double stranded DNA

Although Applicants note that Felgner et al do not describe including a moiety that interacts with transcription factors in the construct and submit that the activator domain of a transcription factor (natural or artificial) interacts directly with the transcription machinery (the RNA Pol II complex), not endogenous transcription factors, as discussed above, the claims do not specifically recite the limitation of gene-specific regulatory factors and do not exclude elements of the transcription machinery as the regulatory or transcription factors. As noted in the above discussion, the teaching of Arora et al is used to introduce the concept of attaching a linking moiety, not specific artificial transcription factors.

Applicants submit that Felgner et al's approach can only evaluate compounds for their ability to act as an <u>activator domain</u> that interacts directly with the transcription machinery, and not with gene-specific transcription factors themselves. Again as discussed above, the claims do not specifically recite the limitation of gene-specific regulatory factors and do not exclude elements of the transcription machinery as the regulatory or transcription factors.

Felgner et al do teach "determining whether binding of the regulatory factor to the binding site defined in the nucleic acid target is modulated by the presence of the test compound." At column 4, lines 53-64, Felgner et al teach a method for screening compounds that activate transcription comprising linking a compound to a PNA, hybridizing a plasmid encoding a reporter gene to the PNA containing said linked compound, transfecting a cell with the plasmid-PNA-compound complex; determining the level of expression of the reporter gene, and comparing the level of expression of

the reporter gene to the level of expression of the reporter gene in a cell transfected with the plasmid-PNA complex, wherein an increase in reporter gene expression in the presence of the compound indicates that the compound is an activator of transcription.

Although Applicants submit that the Feigner's construct lacks both a regulatory factor binding site defined in the PNA-DNA construct, column 5, lines 50-60 describes Figure 3 which illustrates the PNA clamp hybridized to a complementary DNA sequence on a pPNA1-CMV plasmid containing PNA binding sites, which meets the limitation of a target sequence proximate to but not within a transcription factor binding site. The plasmid also comprises Immediate early gene promoter enhancer regions, which absent evidence to the contrary would comprising a transcription factors binding site. Felgner et al teach that the expression plasmids comprise an enhancer and a promoter that binds RNA polymerase II and associated enzymes and other factors with are required to initiate transcription. Felgner et al teach that the function of enhancer sequences is to bind specific intracellular transcription factors which would interact with the transcription complex and increase the transcription rate (see column 8, lines 12-35, in particular).

Therefore, Feigner et al do define a binding site in their plasmid and the claims do not specifically recite the limitation of gene-specific regulatory factors and do not exclude elements of the transcription machinery as the regulatory or transcription factors. Thus, Felgner et al (U.S. Patent No. 6,165,720) in view of Arora et al render obvious claims 1, 3, 8-9, 11, 13, 17-18, 20, 31 and 33.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
Examiner
5/17/2007

CELINE QIAN, PH.D.
PRIMARY EXAMINER